

Claims

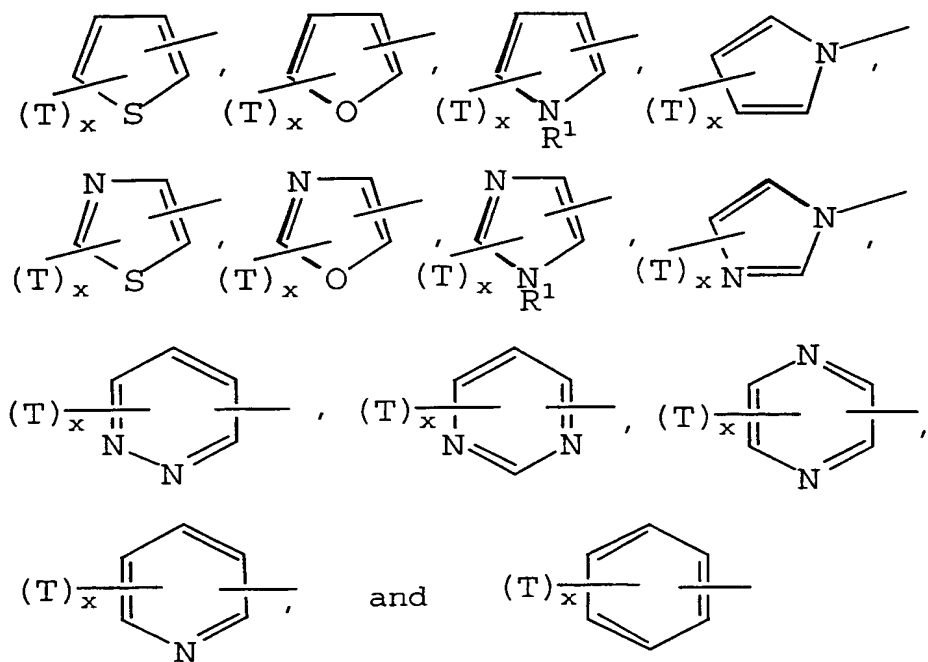
1. Use of compounds of the generalized formula (I):



wherein

- (a) $(T)_x A$ represents a substituted or unsubstituted aromatic or heteroaromatic moiety selected from the group consisting of:

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wherein R^1 represents H or alkyl of 1 - 3 carbons; and

- 15 each T represents a substituent group, independently selected from the group consisting of:

- * the halogens -F, -Cl, -Br, and -I;
- * alkyl of 1 - 10 carbons;
- * haloalkyl of 1 - 10 carbons;
- 20 * haloalkoxy of 1 - 10 carbons;

- * alkenyl of 2 - 10 carbons;
- * alkynyl of 2 - 10 carbons;
- * $-(CH_2)_pQ$, wherein
p is 0 or an integer 1 - 4,
- 5 * -alkenyl-Q, wherein
said alkenyl moiety comprises 2 - 4 carbons, and
- * -alkynyl-Q, wherein
said alkynyl moiety comprises 2 - 7 carbons; and

10 Q is selected from the group consisting of aryl of 6 - 10 carbons,
heteroaryl comprising 4 - 9 carbons and at least one N, O, or S
heteroatom, -CN, -CHO, -NO₂, -CO₂R², -OCOR², -SOR³,
-SO₂R³, -CON(R⁴)₂, -SO₂N(R⁴)₂, -C(O)R², -N(R⁴)₂,
-N(R²)COR², -N(R²)CO₂R³, -N(R²)CON(R⁴)₂, -CHN₄, -OR⁴,
15 and -SR⁴;

wherein

R² represents H;

20 alkyl of 1 - 6 carbons;
aryl of 6 - 10 carbons;
heteroaryl comprising 4 - 9 carbons and at least one N, O,
or S heteroatom; or
arylalkyl in which the aryl portion contains 6 - 10 carbons
25 and the alkyl portion contains 1 - 4 carbons; or
heteroaryl-alkyl in which the heteroaryl portion comprises
4 - 9 carbons and at least one N, O, or S heteroatom and
the alkyl portion contains 1 - 4 carbons;

R³ represents alkyl of 1 - 4 carbons;

30 aryl of 6 - 10 carbons;

- heteroaryl comprising 4 - 9 carbons and at least one N, O,
or S heteroatom; or
arylalkyl in which the aryl portion contains 6 - 10 carbons
and the alkyl portion contains 1 - 4 carbons; or
5 heteroaryl-alkyl in which the heteroaryl portion comprises
4 - 9 carbons and at least one N, O, or S heteroatom and
the alkyl portion contains 1 - 4 carbons;
 R^4 represents H;
alkyl of 1 - 12 carbons;
10 aryl of 6 - 10 carbons;
heteroaryl comprising 4 - 9 carbons and at least one N, O,
or S heteroatom;
arylalkyl in which the aryl portion contains 6 - 10 carbons
and the alkyl portion contains 1 - 4 carbons;
15 heteroaryl-alkyl in which the heteroaryl portion comprises
4 - 9 carbons and at least one N, O, or S heteroatom and
the alkyl portion contains 1 - 4 carbons;
alkenyl of 2 - 12 carbons;
alkynyl of 2 - 12 carbons;
20 $-(C_qH_{2q}O)_rR^5$ wherein q is 1-3; r is 1 - 3; and R^5 is H
provided q is greater than 1, or alkyl of 1 - 4 carbons, or
phenyl;
alkylenethio terminated with H, alkyl of 1-4 Carbons, or
phenyl;
25 alkyleneamino terminated with H, alkyl of 1-4 carbons, or
phenyl;
 $-(CH_2)_sX$ wherein s is 1 - 3 and X is halogen;
 $-C(O)OR^2$; or
 $-C(O)R^2$;
30 and with the provisos that a) when two R^4 groups are situated
on a nitrogen, they may be joined by a bond to form a

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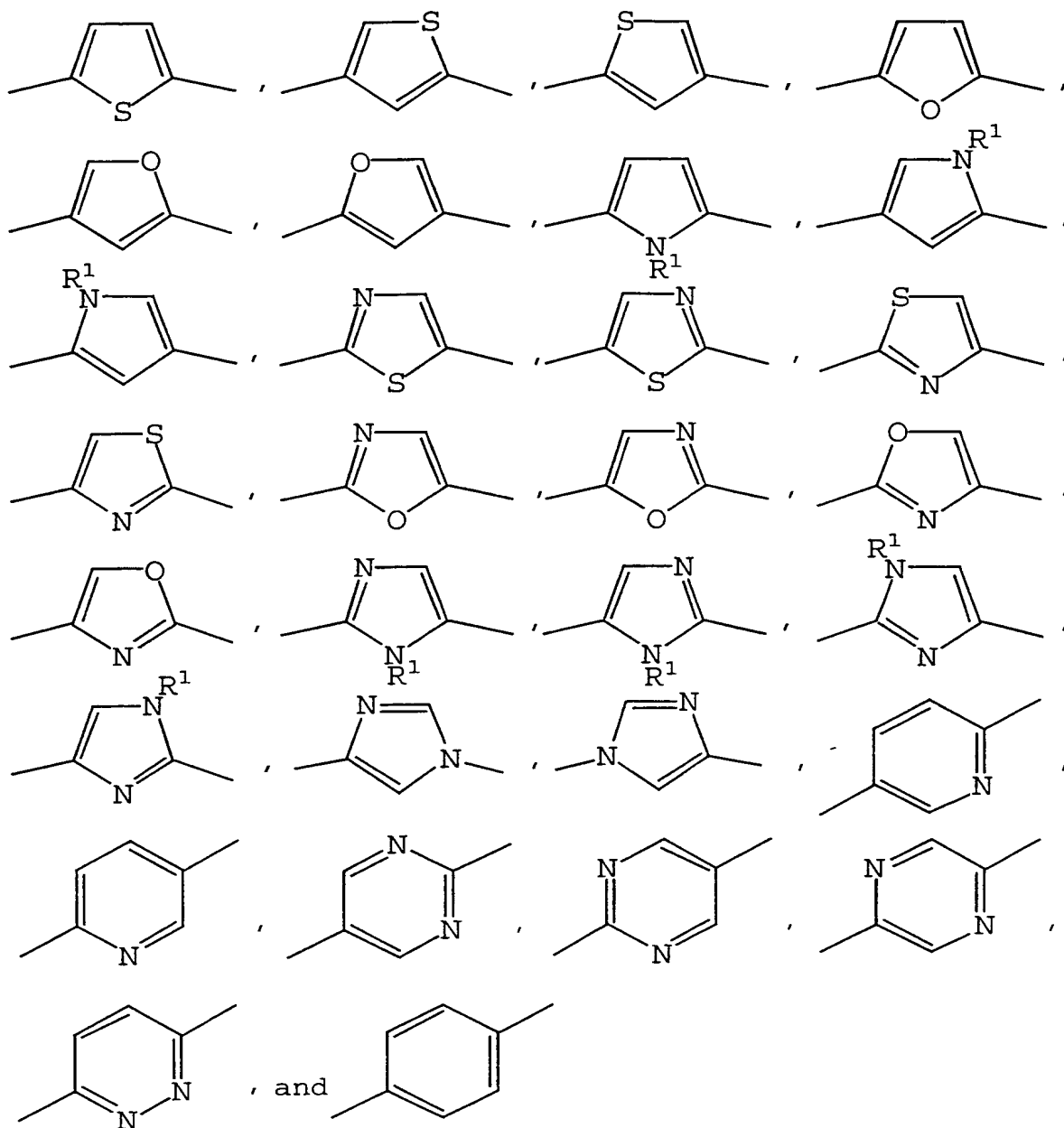
heterocycle, and b) unsaturation in a moiety which is attached to Q or which is part of Q is separated from any N, O, or S of Q by at least one carbon atom, and

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x is 0, 1, or 2;

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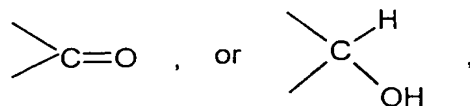
- (b) B represents a bond or an optionally substituted aromatic or hetero-aromatic ring containing 0-2 substituents T, which substituents T may independently have the meaning specified under (a), the B rings being selected from the group consisting of:



wherein R^1 is as defined above and each R^1 may be the same or different:

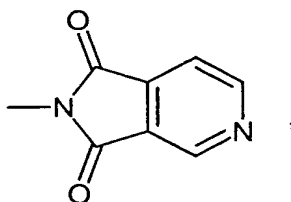
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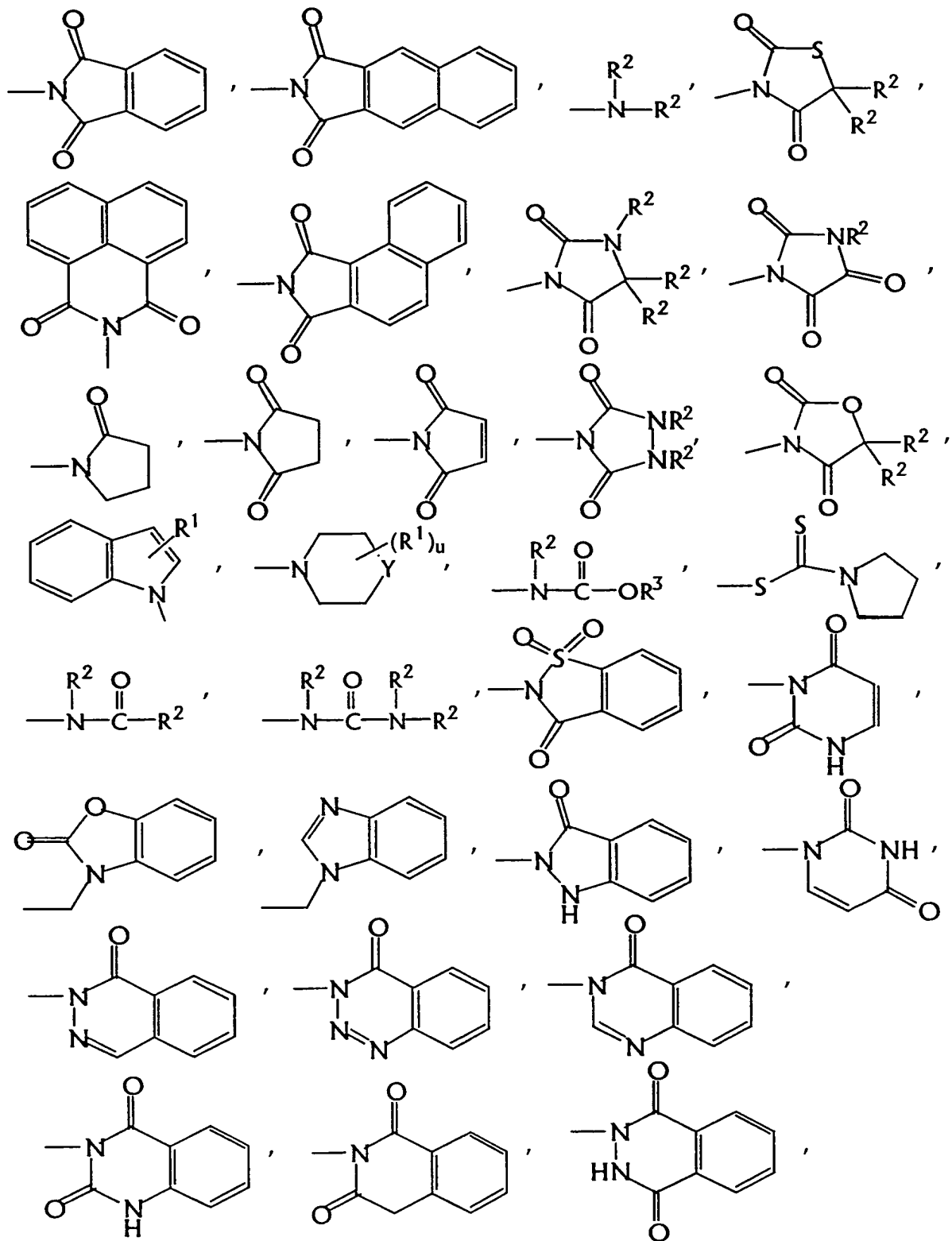
(c) D represents



- (d) E represents a chain of n carbon atoms bearing m substituents R^6 , wherein said R^6 groups are independent substituents, or constitute spiro or nonspiro rings in which a) two groups R^6 are joined, and taken together with the chain atom(s) to which said two R^6 group(s) are attached, and any intervening chain atoms, constitute a 3 - 7 membered ring, or b) one group R^6 is joined to the chain on which said one group R^6 resides, and taken together with the chain atom(s) to which said R^6 group is attached, and any intervening chain atoms, constitutes a 3 - 7 membered ring; and wherein
- n is 2 or 3;
- m is an integer of 1 - 3;
- each group R^6 is independently selected from the group consisting of:
- * fluorine;
 - * hydroxyl, with the proviso that a single carbon may bear no more than one hydroxyl substituent
 - * alkyl of 1 - 10 carbons;
 - * aryl of 6 - 10 carbons;
 - * heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;
 - * arylalkyl wherein the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 8 carbons;

- 5
- * heteroaryl-alkyl wherein the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom, and the alkyl portion contains 1 - 8 carbons;
- 10
- * alkenyl of 2 - 10 carbons;
 - * aryl-alkenyl wherein the aryl portion contains 6 - 10 carbons and the alkenyl portion contains 2 - 5 carbons;
- 15
- * heteroaryl-alkenyl wherein the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkenyl portion contains 2 - 5 carbons;
 - * alkynyl of 2 - 10 carbons;
 - * aryl-alkynyl wherein the aryl portion contains 6 - 10 carbons and the alkynyl portion contains 2 - 5 carbons;
 - * heteroaryl-alkynyl wherein the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkynyl portion contains 2 - 5 carbons;
- 20
- * $-(CH_2)_tR^7$ wherein
t is 0 or an integer of 1 - 5; and
 R^7 is selected from the group consisting of





and corresponding heteroaryl moieties in which the aryl portion of an aryl-containing R^7 group comprises 4 - 9 carbons and at least one N, O, or S heteroatom;

wherein

5

Y represents O or S;

R^1 , R^2 , and R^3 are as defined above and each R^1 , R^2 or R^3 may be the same or different; and

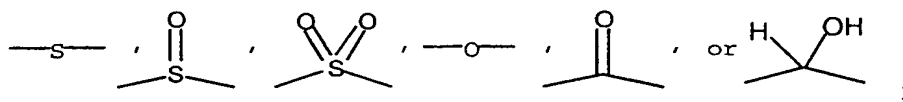
u is 0, 1, or 2; and

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* $-(CH_2)_vZR^8$ wherein

v is 0 or an integer of 1 to 4; and

Z represents



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R^8 is selected from the group consisting of:

alkyl of 1 to 12 carbons;

aryl of 6 to 10 carbons;

heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;

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arylalkyl wherein the aryl portion contains 6 to 10 carbons and the alkyl portion contains 1 to 4 carbons;

heteroaryl-alkyl wherein the aryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

25

$-C(O)R^9$ wherein R^9 represents alkyl of 2 - 6 carbons, aryl of 6 - 10 carbons, heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, or arylalkyl in which the aryl portion contains 6 - 10 carbons or is heteroaryl comprising 4 - 9

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carbons and at least one N, O, or S heteroatom, and the alkyl portion contains 1 - 4 carbons;

and with the provisos that

- when R^8 is $-C(O)R^9$, Z is S or O;
- 5 - when Z is O, R^8 may also be $-(C_qH_{2q}O)_rR^5$ wherein q, r, and R^5 are as defined above; and

* $-(CH_2)_wSiR^{10}_3$ wherein

w is an integer of 1 to 3; and

10 R^{10} represents alkyl of 1 to 2 carbons;

and with the proviso that

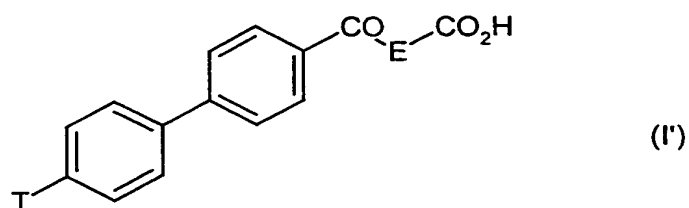
- aryl or heteroaryl portions of any of said T or R^6 groups optionally may bear up to two substituents selected from the group consisting of
- 15 $-(CH_2)_yC(R^4)(R^3)OH$, $-(CH_2)_yOR^4$, $-(CH_2)_ySR^4$, $-(CH_2)_yS(O)R^4$,
 $-(CH_2)_yS(O)_2R^4$, $-(CH_2)_ySO_2N(R^4)_2$, $-(CH_2)_yN(R^4)_2$,
 $-(CH_2)_yN(R^4)COR^3$, $-OC(R^4)_2O-$ in which both oxygen atoms are
 connected to the aryl ring, $-(CH_2)_yCOR^4$, $-(CH_2)_yCON(R^4)_2$,
 $-(CH_2)_yCO_2R^4$, $-(CH_2)_yOCOR^4$, -halogen, -CHO, -CF₃, -NO₂, -CN,
20 and $-R^3$, wherein
 y is 0 - 4; and
 R^3 and R^4 are defined as above, and each R^3 or R^4 may be the same or
 different; and any two R^4 which are attached to one nitrogen may be
 joined to form a heterocycle;

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and pharmaceutically acceptable salts and prodrugs thereof for the manufacturing of drugs for the treatment and prevention of multiple sclerosis.

2. Use according to claim 1 of compounds of the general formula (I')

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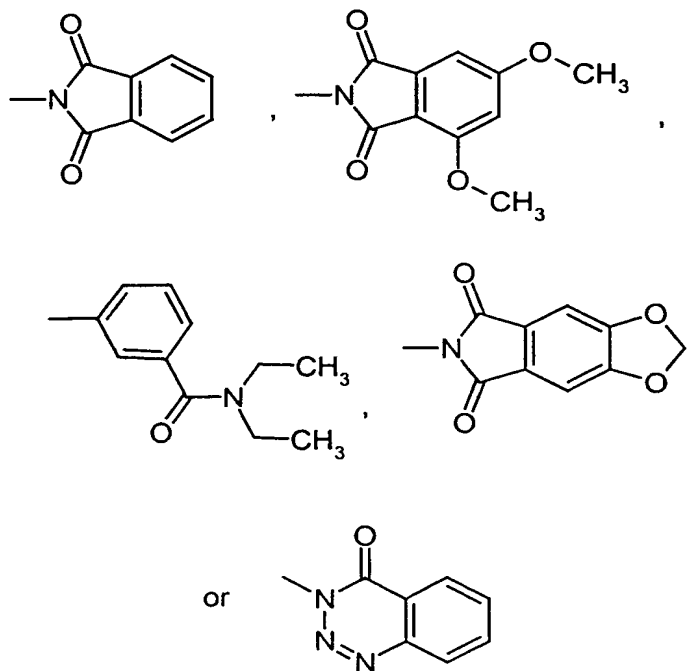


wherein

T is (C₁-C₄)-alkyl, (C₁-C₄)-alkoxy, chloride, bromide, fluoride, acetoxy, hydroxy, cyano, trifluoromethyl or trifluoromethoxy,

CO-E-CO₂H represents a 3-carboxyl-5-(R⁷)-pentan-1-on-1-yl- or a [2-carboxyl-3-(R⁷)-methyl-cyclopentan-1-yl]-carbonyl-residue, wherein

R⁷ represents a group of the formula



and their salts.

3. Use according to claim 2, characterized in that the enantiomer of a pair of enantiomers at a chiral center adjacent to the carboxylic acid moiety of the

group of the formula CO-E-CO₂H in compounds of the general formula (I') more potently inhibits MMP-2 and/or MMP-9.

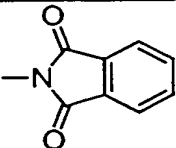
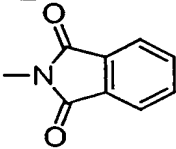
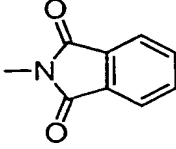
4. Use according to claim 1, wherein the compound is selected from the group consisting of

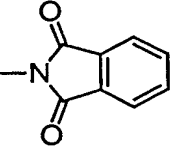
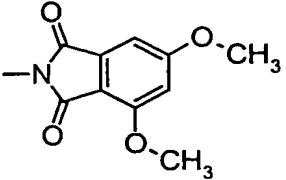
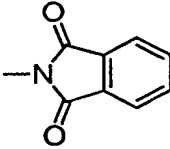
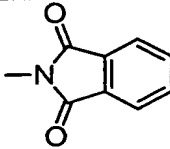
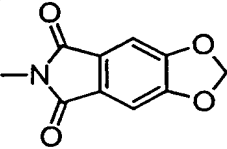
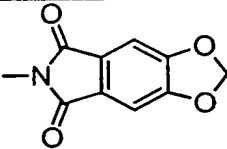
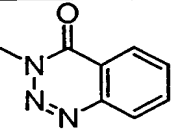
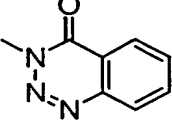
(+)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-(4'-ethoxy[1,1'-biphenyl]-4-yl)-4-oxobutanoic acid,

(+)-4-(4'-chloro[1,1'-biphenyl]-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-oxobutanoic acid,

or a salt thereof.

5. Compounds of the general formula (I'), wherein CO-E-CO₂H represents a 3-carboxyl-5-R⁷-pentan-1-on-1-yl-residue, and wherein T and R⁷ have the meaning indicated in the following table:

T	R ⁷	racemate, (+)- or (-)-enantiomer	
OEt		(+)	;
OEt		(-)	;
OAc		rac	;

T	R ⁷	racemate, (+)- or (-)-enantiomer	
OH		rac	;
Cl		rac	;
Br		(+)	;
Br		(-)	;
Cl		(+)	;
Cl		(-)	;
CN		rac	or
OCF ₃		rac	.

6. Pharmaceutical composition which as active constituent contains at least one compound according to claim 5 mixed together with at least one pharmaceutically tolerable essentially non-toxic vehicle or excipient.
- 5 7. Process for the preparation of a pharmaceutical composition according to claim 6.
8. Compound according to claim 5 for use as a medicament in the treatment of humans or animals.